



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|---|---|--|
| (51) International Patent Classification ⁷ : A61K 41/00 | A1 | (11) International Publication Number: WO 00/01411 (43) International Publication Date: 13 January 2000 (13.01.00) |
| (21) International Application Number: PCT/EP99/04545 (22) International Filing Date: 30 June 1999 (30.06.99) (30) Priority Data: 98202257.6 6 July 1998 (06.07.98) EP 98204330.9 18 December 1998 (18.12.98) EP (71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventors; and (75) Inventors/Applicants (for US only): VAN GINCKEL, Robert, Franciscus [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). FLOREN, Wim, Joanna [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). END, David, William [US/US]; Janssen Research Foundation, Welsh and McKean Roads, Spring House, PA 19477-0776 (US). WOUTERS, Walter, Boudewijn, Leopold [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). | (74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Dept. - ext. 3547, Turnhoutseweg 30, B-2340 Beerse (BE). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> | |
| (54) Title: FARNESYL PROTEIN TRANSFERASE INHIBITORS WITH <i>IN VIVO</i> RADIOSENSITIZING PROPERTIES | | |
| (57) Abstract The present invention is concerned with the finding that farnesyl protein transferase inhibitors have radiosensitizing properties which makes them useful for preparing a pharmaceutical composition for administration before, during or after irradiation of a tumor for treating cancer <i>in vivo</i> . | | |

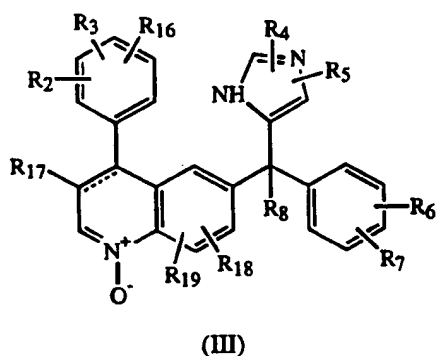
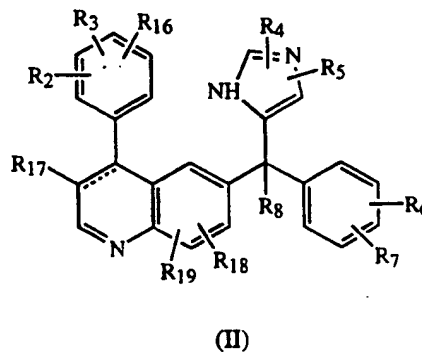
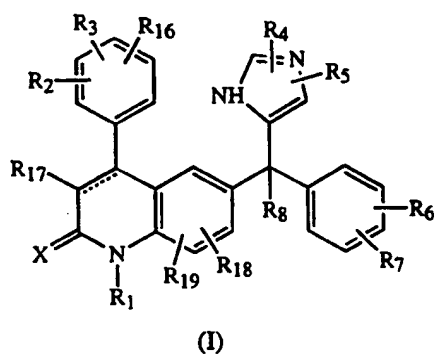
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | Republic of Korea | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

Farnesyl protein transferase
inhibitors with *in vivo* radiosensitizing properties

- 5 The present invention is concerned with the finding that farnesyl protein transferase inhibitors have radiosensitizing properties which makes them useful for preparing a pharmaceutical composition for administration before, during or after irradiation of a tumor for treating cancer *in vivo*.
- 10 WO-97/21701 describes the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting (imidazoly-5-yl)methyl-2-quinolinone derivatives of formulas (I), (II) and (III), as well as intermediates of formula (II) and (III) that are metabolized *in vivo* to the compounds of formula (I). The compounds of formulas (I),
- 15 (II) and (III) are represented by



the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein the dotted line represents an optional bond;

- 20 X is oxygen or sulfur;
R¹ is hydrogen, C₁₋₁₂alkyl, Ar¹, Ar²C₁₋₆alkyl, quinolinylC₁₋₆alkyl, pyridylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)

aminoC₁₋₆alkyl, aminoC₁₋₆alkyl,

or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹,

wherein Alk¹ is C₁₋₆alkanediyl,

R⁹ is hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, amino, C₁₋₈alkylamino or

5 C₁₋₈alkylamino substituted with C₁₋₆alkyloxycarbonyl;

R², R³ and R¹⁶ each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl,

C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, aminoC₁₋₆alkyl-

oxy, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar¹, Ar²C₁₋₆alkyl, Ar²oxy,

Ar²C₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, trihalomethyl,

10 trihalomethoxy, C₂₋₆alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R² and R³ taken together may form a bivalent radical of formula

-O-CH₂-O- (a-1),

-O-CH₂-CH₂-O- (a-2),

15 -O-CH=CH- (a-3),

-O-CH₂-CH₂- (a-4),

-O-CH₂-CH₂-CH₂- (a-5), or

-CH=CH-CH=CH- (a-6);

R⁴ and R⁵ each independently are hydrogen, halo, Ar¹, C₁₋₆alkyl, hydroxyC₁₋₆alkyl,

20 C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, hydroxycarbonyl,

C₁₋₆alkyloxycarbonyl, C₁₋₆alkylS(O)C₁₋₆alkyl or C₁₋₆alkylS(O)₂C₁₋₆alkyl;

R⁶ and R⁷ each independently are hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy,

Ar²oxy, trihalomethyl, C₁₋₆alkylthio, di(C₁₋₆alkyl)amino, or

when on adjacent positions R⁶ and R⁷ taken together may form a bivalent radical

25 of formula

-O-CH₂-O- (c-1), or

-CH=CH-CH=CH- (c-2);

R⁸ is hydrogen, C₁₋₆alkyl, cyano, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl-

carbonylC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, carboxy-

30 C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)amino-

C₁₋₆alkyl, imidazolyl, haloC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminocarbonyl-

C₁₋₆alkyl, or a radical of formula

-O-R¹⁰ (b-1),

-S-R¹⁰ (b-2),

35 -N-R¹¹R¹² (b-3),

wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹, Ar²C₁₋₆alkyl,

C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical or formula

-3-

-Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;R¹¹ is hydrogen, C₁₋₁₂alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹² is hydrogen, C₁₋₆alkyl, C₁₋₁₆alkylcarbonyl, C₁₋₆alkyloxy-carbonyl, C₁₋₆alkylaminocarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkylcarbonylC₁₋₆alkyl, a natural amino acid, Ar¹carbonyl, Ar²C₁₋₆alkylcarbonyl, aminocarbonylcarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy, C₁₋₆alkyloxy, aminocarbonyl, di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, amino, C₁₋₆alkylamino, C₁₋₆alkylcarbonylamino, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

wherein Alk² is C₁₋₆alkanediyl;

R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, hydroxyC₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁴ is hydrogen, C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

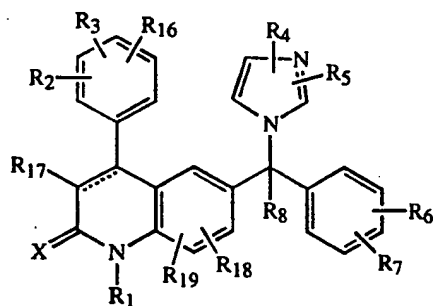
R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁷ is hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, Ar¹;R¹⁸ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;R¹⁹ is hydrogen or C₁₋₆alkyl;

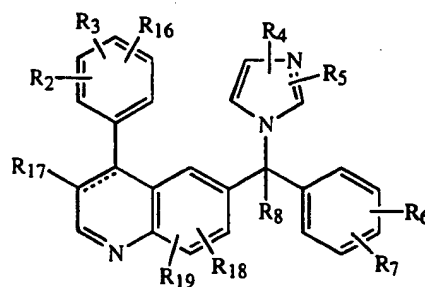
20 Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo; and

Ar² is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo.

25 WO-97/16443 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IV), as well as intermediates of formula (V) and (VI) that are metabolized *in vivo* to the compounds of formula (IV). The compounds of formulas (IV), (V) and (VI) are represented by

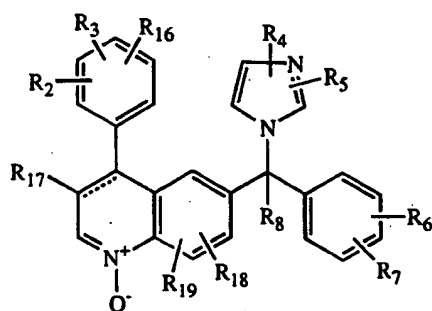


(IV)



(V)

-4-



(VI)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

5 X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12} alkyl, Ar^1 , Ar^2C_{1-6} alkyl, quinolinyl C_{1-6} alkyl, pyridyl C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, amino C_{1-6} alkyl,

or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$,

10 wherein Alk^1 is C_{1-6} alkanediyl,

R^9 is hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, amino, C_{1-8} alkylamino or C_{1-8} alkylamino substituted with C_{1-6} alkyloxycarbonyl;

R^2 and R^3 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , Ar^2C_{1-6} alkyl, Ar^2 oxy, Ar^2C_{1-6} alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6} alkenyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

- 20 $-O-CH_2-O-$ (a-1),
 $-O-CH_2-CH_2-O-$ (a-2),
 $-O-CH=CH-$ (a-3),
 $-O-CH_2-CH_2-$ (a-4),
 $-O-CH_2-CH_2-CH_2-$ (a-5), or
 25 $-CH=CH-CH=CH-$ (a-6);

R^4 and R^5 each independently are hydrogen, Ar^1 , C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2C_{1-6}$ alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy or Ar^2 oxy;

30

R⁸ is hydrogen, C₁₋₆alkyl, cyano, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl-carbonylC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, hydroxy-carbonylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)-aminoC₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, Ar¹, Ar²C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl;

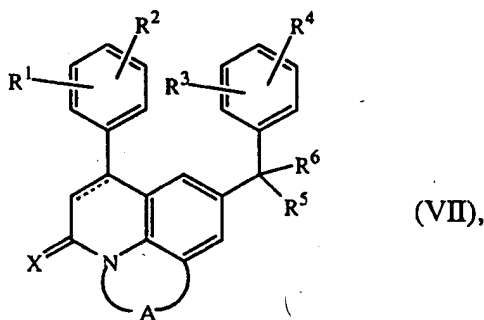
R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;

R¹¹ is hydrogen or C₁₋₆alkyl;

Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo;

10 Ar² is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo.

15 PCT/EP98/01296, filed 3 March 1998, concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (VII)



the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

20 the dotted line represents an optional bond;

X is oxygen or sulfur;

-A- is a bivalent radical of formula

$$-\text{CH}=\text{CH}- \quad (\text{a-1}),$$
$$-\text{CH}_2-\text{S}- \quad (\text{a-6}),$$
$$-\text{CH}_2-\text{CH}_2- \quad (\text{a-2}),$$
$$-\text{CH}_2-\text{CH}_2-\text{S}- \quad (\text{a-7}),$$

25 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ (a-3),

$$-\text{CH}=\text{N}- \quad (\text{a-8}),$$
$$-\text{CH}_2-\text{O}- \quad (\text{a-4}),$$

-N=N- (a-9), or

$$-\text{CH}_2-\text{CH}_2-\text{O}- \quad (\text{a-5}),$$

-CO-NH- (a-10);

wherein optionally one hydrogen atom may be replaced by C₁₋₄alkyl or Ar¹;

30 R¹ and R² each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl, trihalomethyl, trihalomethoxy, C₂₋₆alkenyl, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, aminoC₁₋₆alkyloxy, mono- or

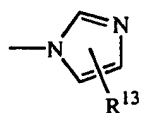
di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar², Ar²-C₁₋₆alkyl, Ar²-oxy, Ar²-C₁₋₆alkyloxy;
or when on adjacent positions R¹ and R² taken together may form a bivalent
radical of formula

- 5 -O-CH₂-O- (b-1),
 -O-CH₂-CH₂-O- (b-2),
 -O-CH=CH- (b-3),
 -O-CH₂-CH₂- (b-4),
 -O-CH₂-CH₂-CH₂- (b-5), or
 -CH=CH-CH=CH- (b-6);

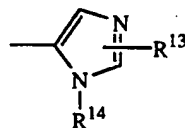
- 10 R³ and R⁴ each independently are hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy,
 Ar³-oxy, C₁₋₆alkylthio, di(C₁₋₆alkyl)amino, trihalomethyl, trihalomethoxy, or
 when on adjacent positions R³ and R⁴ taken together may form a bivalent radical
 of formula

- O-CH₂-O- (c-1),
15 -O-CH₂-CH₂-O- (c-2), or
 -CH=CH-CH=CH- (c-3);

R⁵ is a radical of formula



(d-1),



(d-2),

wherein R¹³ is hydrogen, halo, Ar⁴, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxy.

- 20 C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, C₁₋₆alkyloxycarbonyl,
 C₁₋₆alkylS(O)C₁₋₆alkyl or C₁₋₆alkylS(O)₂C₁₋₆alkyl;

R¹⁴ is hydrogen, C₁₋₆alkyl or di(C₁₋₄alkyl)aminosulfonyl;

- R⁶ is hydrogen, hydroxy, halo, C₁₋₆alkyl, cyano, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl,
 cyanoC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl,
25 aminocarbonylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, C₁₋₆alkylcarbonyl-
 C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, Ar⁵,
 Ar⁵-C₁₋₆alkyloxyC₁₋₆alkyl; or a radical of formula

- O-R⁷ (e-1),
 -S-R⁷ (e-2),
30 -N-R⁸R⁹ (e-3),

wherein R⁷ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar⁶, Ar⁶-C₁₋₆alkyl,
 C₁₋₆alkyloxycarbonylC₁₋₆alkyl,

or a radical of formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

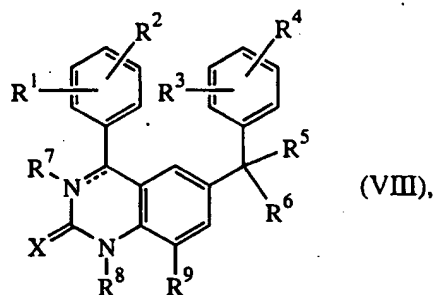
R⁸ is hydrogen, C₁₋₆alkyl, Ar⁷ or Ar⁷-C₁₋₆alkyl;

-7-

- 5 R^9 is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxy, carbonyl, C_{1-6} alkylaminocarbonyl, Ar^8 , Ar^8-C_{1-6} alkyl, C_{1-6} alkylcarbonyl- C_{1-6} alkyl, Ar^8 -carbonyl, Ar^8-C_{1-6} alkylcarbonyl, aminocarbonyl-carbonyl, C_{1-6} alkyloxy- C_{1-6} alkylcarbonyl, hydroxy, C_{1-6} alkyloxy, aminocarbonyl, di(C_{1-6} alkyl)amino- C_{1-6} alkylcarbonyl, amino, C_{1-6} alkylamino, C_{1-6} alkylcarbonylamino, or a radical or formula $-Alk-OR^{10}$ or $-Alk-NR^{11}R^{12}$; wherein Alk is C_{1-6} alkanediyl;
- 10 R^{10} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, hydroxy- C_{1-6} alkyl, Ar^9 or Ar^9-C_{1-6} alkyl;
- R^{11} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, Ar^{10} or $Ar^{10}-C_{1-6}$ alkyl;
- R^{12} is hydrogen, C_{1-6} alkyl, Ar^{11} or $Ar^{11}-C_{1-6}$ alkyl; and Ar^1 to Ar^{11} are each independently selected from phenyl; or
- 15 phenyl substituted with halo, C_{1-6} alkyl, C_{1-6} alkyloxy or trifluoromethyl.

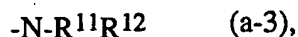
PCT/EP98/02357, filed 17 April 1998, concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of

20 formula (VIII)



- the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein
- the dotted line represents an optional bond;
- 25 X is oxygen or sulfur;
- R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl, trihalomethyl, trihalomethoxy, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy- C_{1-6} alkyloxy, C_{1-6} alkyloxy- C_{1-6} alkyloxy, C_{1-6} alkyloxy- C_{1-6} alkylcarbonyl, amino- C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino- C_{1-6} alkyloxy, Ar^1 , Ar^1-C_{1-6} alkyl, Ar^1 -oxy or Ar^1-C_{1-6} alkyloxy;
- 30 R^3 and R^4 each independently are hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, Ar^1 -oxy, C_{1-6} alkylthio, di(C_{1-6} alkyl)amino, trihalomethyl or trihalomethoxy;

R^5 is hydrogen, halo, C_{1-6} alkyl, cyano, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, cyano- C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, C_{1-6} alkylcarbonyl- C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, Ar^1 , Ar^1C_{1-6} alkyloxy C_{1-6} alkyl; or a radical of formula



wherein R^{10} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, Ar^1 , Ar^1C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, or a radical of formula $-Alk-OR^{13}$ or $-Alk-NR^{14}R^{15}$;

R^{11} is hydrogen, C_{1-6} alkyl, Ar^1 or Ar^1C_{1-6} alkyl;

R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylaminocarbonyl, Ar^1 , Ar^1C_{1-6} alkyl, C_{1-6} alkylcarbonyl- C_{1-6} alkyl, Ar^1 carbonyl, Ar^1C_{1-6} alkylcarbonyl, aminocarbonylcarbonyl, C_{1-6} alkyloxy C_{1-6} alkylcarbonyl, hydroxy, C_{1-6} alkyloxy, aminocarbonyl, di(C_{1-6} alkyl)amino C_{1-6} alkylcarbonyl, amino, C_{1-6} alkylamino, C_{1-6} alkylcarbonylamino, or a radical or formula $-Alk-OR^{13}$ or $-Alk-NR^{14}R^{15}$;

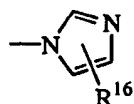
wherein Alk is C_{1-6} alkanediyl;

R^{13} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, hydroxy- C_{1-6} alkyl, Ar^1 or Ar^1C_{1-6} alkyl;

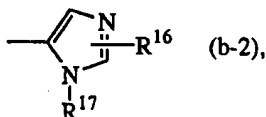
R^{14} is hydrogen, C_{1-6} alkyl, Ar^1 or Ar^1C_{1-6} alkyl;

R^{15} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, Ar^1 or Ar^1C_{1-6} alkyl;

R^6 is a radical of formula



(b-1),



(b-2),

wherein R^{16} is hydrogen, halo, Ar^1 , C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy- C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylthio C_{1-6} alkyl, C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2C_{1-6}$ alkyl;

R^{17} is hydrogen, C_{1-6} alkyl or di(C_{1-4} alkyl)aminosulfonyl;

R^7 is hydrogen or C_{1-6} alkyl provided that the dotted line does not represent a bond;

R^8 is hydrogen, C_{1-6} alkyl or Ar^2CH_2 or Het^1CH_2 ;

R⁹ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo; or

R⁸ and R⁹ taken together to form a bivalent radical of formula

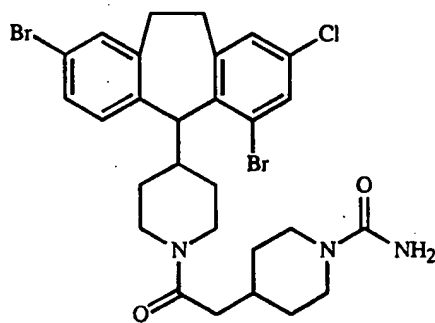
- 5 -CH=CH- (c-1),
 -CH₂-CH₂- (c-2),
 -CH₂-CH₂-CH₂- (c-3),
 -CH₂-O- (c-4), or
 -CH₂-CH₂-O- (c-5);

Ar¹ is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl;

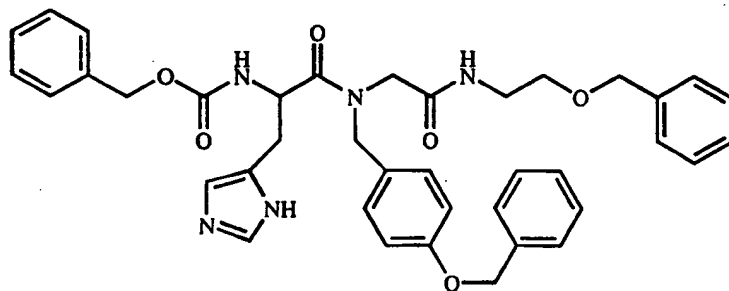
- 10 Ar² is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl; and

Het¹ is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl.

- 15 Other useful farnesyl protein transferase inhibitors have the structure :



SCH-66336



PD-169551

- 20 These farnesyl protein transferase inhibitors decrease the growth of tumors *in vivo* by a direct effect on tumor cell growth but also indirectly, *i.e.* by inhibiting angiogenesis (Rak. J. *et al*, Cancer Research, 55, 4575-4580, 1995). Consequently, treatment with these inhibitors suppresses solid tumor growth *in vivo* at least in part by inhibiting

-10-

angiogenesis. This being the case, one could expect that treatment with these compounds could result in hypoxic tumors, thereby inducing or causing increased radio-resistance.

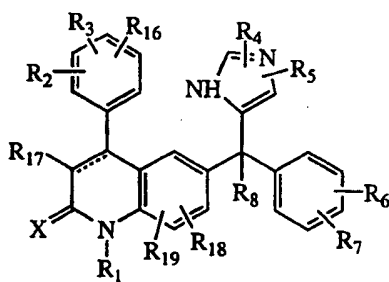
- 5 Unexpectedly, we have now found that that does not happen. On the contrary, it appears that administration of a farnesyl protein transferase inhibitor as described hereinbefore sensitizes tumor cells *in vivo* to irradiation or ionizing radiation and moreover, resensitizes radioresistant cells. Thus, farnesyl protein transferase inhibitors are useful as *in vivo* radiosensitizing (radiation-sensitizing or radiation-potentiating)
- 10 agents.

The present invention is concerned with the use of at least a farnesyl protein transferase inhibitor for the preparation of a pharmaceutical composition having radiosensitizing properties for administration before, during or after irradiation of a tumor for treating

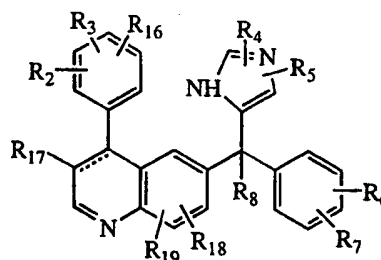
15 cancer *in vivo*.

In particular, the present invention is concerned with the use of at least a farnesyl protein transferase inhibitor for the preparation of a pharmaceutical composition having radiosensitizing properties for administration before, during or after irradiation of a

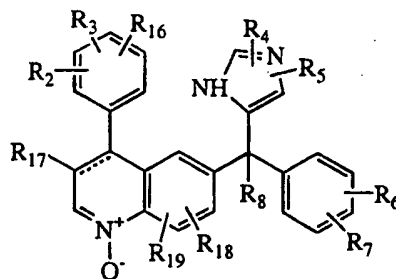
20 tumor for treating cancer *in vivo*, wherein said farnesyl protein transferase inhibitor is an (imidazoly-5-yl)methyl-2-quinolinone derivative of formula (I), or a compound of formula (II) or (III) which is metabolized *in vivo* to the compound of formula (I), said compounds being represented by



(I)



(II)



(III)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

- 5 R^1 is hydrogen, C_{1-12} alkyl, Ar^1 , Ar^2C_{1-6} alkyl, quinolinyl C_{1-6} alkyl, pyridyl C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, amino C_{1-6} alkyl,

or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$, wherein Alk^1 is C_{1-6} alkanediyl,

- 10 R^9 is hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, amino, C_{1-8} alkylamino or C_{1-8} alkylamino substituted with C_{1-6} alkyloxycarbonyl;

R^2 , R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , Ar^2C_{1-6} alkyl, Ar^2 oxy,

- 15 Ar^2C_{1-6} alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6} alkenyl, 4,4-dimethyloxazolyl; or

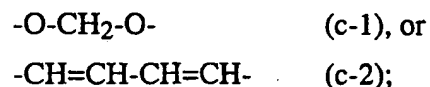
when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

- 20 $-O-CH_2-O-$ (a-1),
 $-O-CH_2-CH_2-O-$ (a-2),
 $-O-CH=CH-$ (a-3),
 $-O-CH_2-CH_2-$ (a-4),
 $-O-CH_2-CH_2-CH_2-$ (a-5), or
 $-CH=CH-CH=CH-$ (a-6);

- 25 R^4 and R^5 each independently are hydrogen, halo, Ar^1 , C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2C_{1-6}$ alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, Ar^2 oxy, trihalomethyl, C_{1-6} alkylthio, di(C_{1-6} alkyl)amino, or

- 30 when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula



- 35 R^8 is hydrogen, C_{1-6} alkyl, cyano, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylcarbonyl C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, carboxy- C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino-

-12-

C₁₋₆alkyl, imidazolyl, haloC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminocarbonyl-C₁₋₆alkyl, or a radical of formula

-O-R¹⁰ (b-1),

-S-R¹⁰ (b-2),

5 -N-R¹¹R¹² (b-3),

wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

R¹¹ is hydrogen, C₁₋₁₂alkyl, Ar¹ or Ar²C₁₋₆alkyl;

10 R¹² is hydrogen, C₁₋₆alkyl, C₁₋₁₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkylcarbonyl-C₁₋₆alkyl, a natural amino acid, Ar¹carbonyl, Ar²C₁₋₆alkylcarbonyl, aminocarbonylcarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy, C₁₋₆alkyloxy, aminocarbonyl, di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, 15 amino, C₁₋₆alkylamino, C₁₋₆alkylcarbonylamino, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

wherein Alk² is C₁₋₆alkanediyl;

R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, hydroxyC₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

20 R¹⁴ is hydrogen, C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁷ is hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, Ar¹;

R¹⁸ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;

R¹⁹ is hydrogen or C₁₋₆alkyl;

25 Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo; and

Ar² is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo.

30 In formulas (I), (II) and (III), R⁴ or R⁵ may also be bound to one of the nitrogen atoms in the imidazole ring. In that case the hydrogen on the nitrogen is replaced by R⁴ or R⁵ and the meaning of R⁴ and R⁵ when bound to the nitrogen is limited to hydrogen, Ar¹, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylS(O)C₁₋₆alkyl, C₁₋₆alkylS(O)₂C₁₋₆alkyl.

35

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C₁₋₆alkyl defines straight and branched chained saturated hydrocarbon

radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl and the like; C₁₋₈alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C₁₋₆alkyl as well as the higher homologues thereof containing 7 or 8 carbon atoms such as, for example heptyl or octyl; C₁₋₁₂alkyl again encompasses C₁₋₈alkyl and the higher homologues thereof containing 9 to 12 carbon atoms, such as, for example, nonyl, decyl, undecyl, dodecyl; C₁₋₁₆alkyl again encompasses C₁₋₁₂alkyl and the higher homologues thereof containing 13 to 16 carbon atoms, such as, for example, tridecyl, tetradecyl, pentadecyl and hexadecyl; C₂₋₆alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; C₁₋₆alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof. The term "C(=O)" refers to a carbonyl group, "S(O)" refers to a sulfoxide and "S(O)₂" to a sulfon. The term "natural amino acid" refers to a natural amino acid that is bound via a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of the amino acid and the amino group of the remainder of the molecule. Examples of natural amino acids are glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine.

The pharmaceutically acceptable acid or base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and non-toxic base addition salt forms which the compounds of formulas (I), (II) and (III) are able to form. The compounds of formulas (I), (II) and (III) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The compounds of formulas (I), (II) and (III) which have acidic properties may be converted in their pharmaceutically acceptable base addition salts by treating said acid form with a suitable organic or inorganic base. Appropriate base salt forms comprise,

for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

5

The terms acid or base addition salt also comprise the hydrates and the solvent addition forms which the compounds of formulas (I), (II) and (III) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

- 10 The term stereochemically isomeric forms of compounds of formulas (I), (II) and (III), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formulas (I), (II) and (III) may possess. Unless otherwise mentioned or indicated, the chemical designation
- 15 of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formulas (I), (II) and (III) both in pure form or in admixture with each other are intended to be embraced within the scope of
- 20 the present invention.

Some of the compounds of formulas (I), (II) and (III) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

25

Whenever used hereinafter, the term "compounds of formulas (I), (II) and (III)" is meant to include also the pharmaceutically acceptable acid or base addition salts and all stereoisomeric forms.

- 30 Preferably the substituent R^{18} is situated on the 5 or 7 position of the quinolinone moiety and substituent R^{19} is situated on the 8 position when R^{18} is on the 7-position.

Interesting compounds are these compounds of formula (I) wherein X is oxygen.

- 35 Also interesting compounds are these compounds of formula (I) wherein the dotted line represents a bond, so as to form a double bond.

Another group of interesting compounds are those compounds of formula (I) wherein R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, or a

radical of formula $\text{-Alk}^1\text{-C(=O)-R}^9$, wherein Alk^1 is methylene and R^9 is C_{1-8} alkyl-amino substituted with C_{1-6} alkyloxycarbonyl.

5 Still another group of interesting compounds are those compounds of formula (I) wherein R^3 is hydrogen or halo; and R^2 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, trihalomethoxy or hydroxy C_{1-6} alkyloxy.

10 A further group of interesting compounds are those compounds of formula (I) wherein R^2 and R^3 are on adjacent positions and taken together to form a bivalent radical of formula (a-1), (a-2) or (a-3).

A still further group of interesting compounds are those compounds of formula (I) wherein R^5 is hydrogen and R^4 is hydrogen or C_{1-6} alkyl.

15 Yet another group of interesting compounds are those compounds of formula (I) wherein R^7 is hydrogen; and R^6 is C_{1-6} alkyl or halo, preferably chloro, especially 4-chloro.

20 A particular group of compounds are those compounds of formula (I) wherein R^8 is hydrogen, hydroxy, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, imidazolyl, or a radical of formula $\text{-NR}^{11}\text{R}^{12}$ wherein R^{11} is hydrogen or C_{1-12} alkyl and R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy, C_{1-6} alkyloxy C_{1-6} alkylcarbonyl, or a radical of formula $\text{-Alk}^2\text{-OR}^{13}$ wherein R^{13} is hydrogen or C_{1-6} alkyl.

25 Preferred compounds are those compounds wherein R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, or a radical of formula $\text{-Alk}^1\text{-C(=O)-R}^9$, wherein Alk^1 is methylene and R^9 is C_{1-8} alkylamino substituted with C_{1-6} alkyloxycarbonyl; R^2 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, trihalomethoxy, hydroxy C_{1-6} alkyloxy or Ar^1 ; R^3 is hydrogen; R^4 is methyl bound to the nitrogen in 3-position of the imidazole; R^5 is hydrogen; R^6 is chloro; R^7 is hydrogen; R^8 is hydrogen, hydroxy, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, imidazolyl, or a radical of formula $\text{-NR}^{11}\text{R}^{12}$ wherein R^{11} is hydrogen or C_{1-12} alkyl and R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxy-
35 C_{1-6} alkylcarbonyl, or a radical of formula $\text{-Alk}^2\text{-OR}^{13}$ wherein R^{13} is C_{1-6} alkyl; R^{17} is hydrogen and R^{18} is hydrogen.

Most preferred compounds are

- 4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-2(1*H*)-quinolinone;
- 6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
- 5 6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone;
- 6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride.monohydrate;
- 6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone,
- 10 6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt; and in particular
- (+)-(R)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (Compound 75 in Table 1 of the Experimental
- 15 Part); or a pharmaceutically acceptable acid addition salt thereof.

Farnesyl protein transferase inhibitors can be formulated into pharmaceutical compositions as known in the art ; for the compounds of formulas (I), (II) and (III)

20 suitable examples can be found in WO-97/21701. To prepare the aforementioned pharmaceutical compositions, a therapeutically effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with pharmaceutically acceptable carriers, which may take a wide variety of forms depending on the form of preparation desired for administration.

25 These pharmaceutical compositions are, desirably as unitary dosage forms, administered orally, parenterally, percutaneously, rectally or topically for systemic action, which is preferred, or for topical action. In case of oral liquid pharmaceutical preparations, comprising solutions, suspensions, syrups, elixirs and emulsions, any of the usual pharmaceutical media, such as, for example, water, glycols, oils, alcohols and

30 the like, may be employed, whereas in case of oral solid pharmaceutical preparations, comprising powders, pills, capsules and tablets, excipients such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like may be employed. Because of their ease in administration, tablets and capsules represent the most advantageous oral unit dosage forms, in which case solid pharmaceutical carriers are

35 obviously employed. In case of injectable pharmaceutical compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, such as semipolair solvents, may be included, for example, to aid solubility. Examples of

carriers for injectable solutions comprise saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of the aforementioned formulas may also be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. For the preparation of injectable suspensions, appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment or as a gel. In case of pharmaceutical compositions for rectal administration, any of the usual excipients may be employed, comprising fat based and water soluble excipients, optionally combined with suitable additives, such as suspending or wetting agents. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, lotions, shampoos, tinctures, pastes, ointments, salves, ovules, powders, inhalations, nose sprays, eye drops and the like. Semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used, but application of said compositions may be, for example, also by aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon, or without a propellant such as a pump spray or drops.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, suppositories, ovules, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Preferably, a therapeutically effective amount of the pharmaceutical composition comprising a farnesyl protein transferase inhibitor is administered orally or parenterally. Said therapeutically effective amount is the amount that effectively

sensitizes a tumor in a host to irradiation. On the basis of the current data, it appears that the pharmaceutical composition comprising (+)-(R)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (compound 75) as the active ingredient can be administered orally in an amount of from
5 10 up to 1500 mg/m² daily, either as a single dose or subdivided into more than one dose, or more particularly in an amount of from 100 to 1000 mg/m² daily.

Irradiation means ionizing radiation and in particular gamma radiation, especially that emitted by linear accelerators or by radionuclides that are in common use today. The
10 irradiation of the tumor by radionuclides can be external or internal.

Preferably, the administration of the pharmaceutical composition commences up to one month, in particular up to 10 days or a week, before the irradiation of the tumor. Additionally, it is advantageous to fractionate the irradiation of the tumor and maintain
15 the administration of the pharmaceutical composition in the interval between the first and the last irradiation session.

The amount of farnesyl protein transferase inhibitor, the dose of irradiation and the intermittence of the irradiation doses will depend on a series of parameters such as the
20 type of tumor, its location, the patients' reaction to chemo- or radiotherapy and ultimately is for the physician and radiologists to determine in each individual case.

The present invention also concerns a method of cancer therapy for a host harboring a tumor comprising the steps of
25 - administering a radiation-sensitizing effective amount of a farnesyl protein transferase inhibitor before, during or after
- administering radiation to said host in the proximity to the tumor.

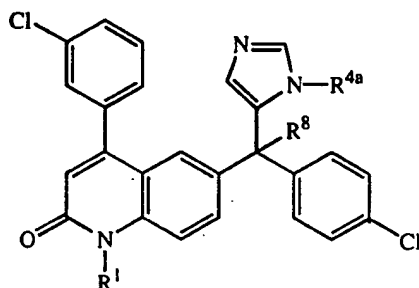
Examples of tumors which may be inhibited, but are not limited to, lung cancer (e.g. adenocarcinoma), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), hematopoietic tumors of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)),
30 thyroid follicular cancer, myelodysplastic syndrome (MDS), tumors of mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumor of the skin (e.g. keratoacanthomas), breast carcinoma, kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal
35

carcinoma.

Experimental part

- The following tables show the formulas of the compounds of formula (I), their physical data, and references to the examples in WO-97/21701 according to which the compounds in question may be prepared. In the pharmacological example, the radiation sensitizing effect of the compounds of formula (I) is illustrated.

Table 1:



10

| Co. No. | Ex. No. | R ¹ | R ^{4a} | R ⁸ | Physical data |
|---------|---------|-----------------|---|---|---|
| 3 | B.1 | CH ₃ | CH ₃ | OH | mp. 233.6°C |
| 4 | B.3 | CH ₃ | CH ₃ | OCH ₃ | mp. 140-160°C; .C ₂ H ₂ O ₄ .H ₂ O |
| 5 | B.6 | CH ₃ | CH ₃ | H | mp. 165°C; .C ₂ H ₂ O ₄ .H ₂ O |
| 6 | B.5 | CH ₃ | CH ₂ CH ₃ | H | mp. 180°C; .C ₂ H ₂ O ₄ .1/2H ₂ O |
| 7 | B.2 | H | CH ₃ | H | mp. 260°C |
| 8 | B.2 | H | (CH ₂) ₃ CH ₃ | OH | - |
| 9 | B.4 | CH ₃ | (CH ₂) ₃ CH ₃ | OH | mp. 174°C |
| 10 | B.3 | H | CH ₃ | OCH ₂ COOC ₂ H ₅ | mp. 185°C; .3/2C ₂ H ₂ O ₄ |
| 11 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₂ N(CH ₃) ₂ | mp. 120°C |
| 12 | B.7 | CH ₃ | CH ₃ | CH ₃ | mp. 210°C; .C ₂ H ₂ O ₄ |
| 13 | B.7 | CH ₃ | CH ₃ | CH ₂ CH ₃ | mp. 196°C; .C ₂ H ₂ O ₄ |
| 14 | B.13 | CH ₃ | CH ₃ | NH ₂ | mp. 220°C |
| 72 | B.13 | CH ₃ | CH ₃ | NH ₂ | .3/2-(E)-C ₄ H ₄ O ₄ |
| 73 | B.13 | CH ₃ | CH ₃ | NH ₂ | .2HCl |
| 74 | B.8b | CH ₃ | CH ₃ | NH ₂ | (A) |
| 75 | B.8b | CH ₃ | CH ₃ | NH ₂ | (+) |

| Co. No. | Ex. No. | R ¹ | R ^{4a} | R ⁸ | Physical data |
|---------|---------|---|---|---|--|
| 15 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₃ OH | mp. 135°C |
| 16 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₂ CH ₃ | mp. 180°C; .C ₂ H ₂ O ₄ .3/2(H ₂ O) |
| 17 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₂ O-C ₆ H ₅ | mp. 144°C; .3/2(C ₂ H ₂ O ₄) |
| 18 | B.2 | H | CH(CH ₃) ₂ | OH | - |
| 19 | B.4 | CH ₃ | CH(CH ₃) ₂ | OH | mp. 254°C |
| 20 | B.2 | H | (CH ₂) ₂ OCH ₃ | OH | mp. 112°C |
| 21 | B.4 | CH ₃ | (CH ₂) ₂ OCH ₃ | OH | mp. 192°C |
| 22 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₂ OH | mp. 198°C |
| 23 | B.8a | CH ₃ | CH ₃ | OH | mp. 150-200°C; (A); .C ₂ H ₂ O ₄ |
| 24 | B.8a | CH ₃ | CH ₃ | OH | mp. 150-200°C; (B); .C ₂ H ₂ O ₄ |
| 25 | B.11 | CH ₃ | CH ₃ | CH ₂ -CN | mp. 154°C |
| 27 | B.2 | H | (CH ₂) ₃ OCH ₃ | OH | - |
| 28 | B.4 | CH ₃ | (CH ₂) ₃ OCH ₃ | OH | mp. 196°C; .H ₂ O |
| 29 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₃ OCH ₂ CH ₃ | mp. 105°C; .3/2(H ₂ O) |
| 31 | B.2 | H | CH ₃ | OH | > 260°C |
| 32 | B.6 | CH ₃ | (CH ₂) ₂ OCH ₃ | H | mp. 140°C; .3/2(C ₂ H ₂ O ₄) |
| 33 | B.6 | CH ₃ | (CH ₂) ₃ OCH ₃ | H | mp. 180°C; .HCl |
| 56 | B.12 | CH ₃ | CH ₃ | -NHCOCH ₃ | .C ₂ H ₂ O ₄ |
| 58 | B.11 | CH ₃ | CH ₃ | -CH ₂ COOCH ₂ CH ₃ | .C ₂ H ₂ O ₄ .3/2(H ₂ O) |
| 60 | B.11 | CH ₃ | CH ₃ | 1-imidazolyl | - |
| 61 | B.21 | CH ₃ | CH ₃ | -NH-CH ₃ | mp. 164°C |
| 65 | B.2 | H | (CH ₂) ₃ SOCH ₃ | OH | .H ₂ O |
| 66 | B.13 | CH ₃ | CH ₃ | -N(CH ₃) ₂ | .2C ₂ H ₂ O ₄ .H ₂ O mp. 160°C |
| 67 | B.13 | CH ₃ | CH ₃ | -NH-(CH ₂) ₂ OCH ₃ | mp. 216°C |
| 68 | B.13 | CH ₃ | CH ₃ | -NH-(CH ₂) ₂ -OH | - |
| 69 | B.7 | CH ₃ | CH ₃ | -CH ₂ Cl | .2C ₂ H ₂ O ₄ mp. 220°C |
| 70 | B.7 | CH ₃ | CH ₃ | -CH ₂ Br | - |
| 71 | * | CH ₃ | CH ₃ | -CH ₂ OH | .2C ₂ H ₂ O ₄ |
| 76 | B.4 | -(CH ₂) ₂ OCH ₃ | CH ₃ | OH | mp. 150°C |

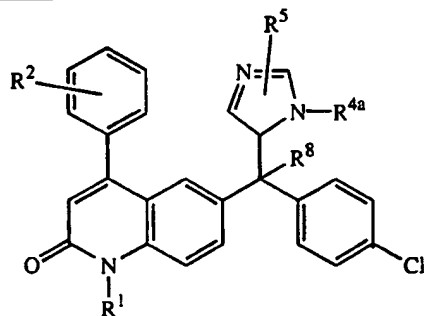
-21-

| Co. No. | Ex. No. | R ¹ | R ^{4a} | R ⁸ | Physical data |
|---------|---------|--|-----------------|---|--|
| 77 | * | CH ₃ | CH ₃ | -CH ₂ OCH ₃ | .2C ₂ H ₂ O ₄ mp. 166°C |
| 78 | B.13 | CH ₃ | CH ₃ | -NH-OCH ₃ | mp. 170°C |
| 79 | B.20 | CH ₃ | CH ₃ | -NH-CONH ₂ | .2H ₂ O |
| 80 | ** | CH ₃ | CH ₃ | -CH ₂ CONH ₂ | - |
| 81 | B.13 | CH ₃ | CH ₃ | -NH-OH | - |
| 82 | B.13 | CH ₃ | CH ₃ | -NH(CH ₂) ₂ N(CH ₃) ₂ | - |
| 83 | B.4 | (CH ₂) ₂ N(CH ₃) ₂ | CH ₃ | OH | .3/2C ₂ H ₂ O ₄ .3/2H ₂ O mp. 200 °C |
| 84 | * | CH ₃ | CH ₃ | -CH ₂ N(CH ₃) ₂ | .C ₂ H ₂ O ₄ mp. 210°C |
| 85 | B.4 | CH ₃ | CH ₃ | -N(CH ₃) ₂ | - |
| 86 | B.4 | CH ₃ | CH ₃ | NHCOCH ₂ N(CH ₃) ₂ | - |
| 87 | B.4 | CH ₃ | CH ₃ | -NH(CH ₂) ₉ CH ₃ | - |
| 88 | B.4 | CH ₃ | CH ₃ | -NH(CH ₂) ₂ NH ₂ | - |
| 89 | B.20 | CH ₃ | CH ₃ | -NHCOCH ₂ OCH ₃ | .HCl mp. 220°C |
| 90 | B.6 | CH ₃ | CH ₃ | H | - |
| 91 | B.20 | CH ₃ | CH ₃ | -NHCOCH ₂ C ₆ H ₅ | .C ₂ H ₂ O ₄ .H ₂ O mp. 170°C |
| 92 | B.20 | CH ₃ | CH ₃ | -NHCOC ₆ H ₅ | mp. 242°C |
| 93 | B.20 | CH ₃ | CH ₃ | -NHCOCONH ₂ | .C ₂ H ₂ O ₄ .H ₂ O mp. 186°C |
| 94 | B.13 | CH ₃ | CH ₃ | -NHC ₆ H ₅ | mp. 165°C |

* : prepared by functional-group transformation of compound 70

** : prepared by functional-group transformation of compound 25

Table 2:



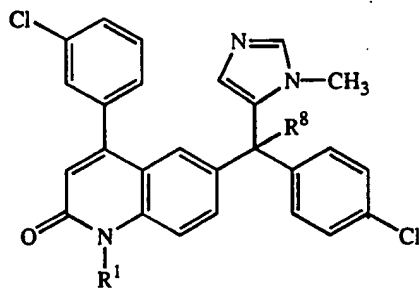
| Co. No. | Ex. No. | R ¹ | R ² | R ^{4a} | R ⁵ | R ⁸ | Physical data |
|---------|---------|-----------------|---|-----------------|-------------------|-----------------|--|
| 1 | B.1 | CH ₃ | H | CH ₃ | H | OH | mp. >250°C |
| 2 | B.5 | CH ₃ | H | CH ₃ | H | H | mp. 100-110°C |
| 26 | B.1 | CH ₃ | 3-Cl | CH ₃ | 2-CH ₃ | OH | mp. 200°C |
| 30 | B.6 | CH ₃ | 3-Cl | CH ₃ | 2-CH ₃ | H | mp. 120-140°C; .3/2(C ₂ H ₂ O ₄).H ₂ O |
| 34 | B.1 | CH ₃ | 3-O-CH ₂ -CH ₃ | CH ₃ | H | OH | mp. 190°C |
| 35 | B.6 | CH ₃ | 3-O-CH ₂ -CH ₃ | CH ₃ | H | H | mp. 160-180°C; .HCl.H ₂ O |
| 36 | B.1 | CH ₃ | 3-O-CH ₃ | CH ₃ | H | OH | mp. 210°C |
| 37 | B.1 | CH ₃ | 3-O-(CH ₂) ₂ -CH ₃ | CH ₃ | H | OH | mp. 150-160°C |
| 38 | B.1 | CH ₃ | 3-O-(CH ₂) ₃ -CH ₃ | CH ₃ | H | OH | mp. 150-160°C |
| 49 | B.1 | CH ₃ | 4-O-CH ₂ -CH ₃ | CH ₃ | H | OH | mp. 184.2°C |
| 50 | B.1 | CH ₃ | 3-O-CH-(CH ₃) ₂ | CH ₃ | H | OH | mp. 147.1°C |
| 51 | B.6 | CH ₃ | 3-O-(CH ₂) ₃ -CH ₃ | CH ₃ | H | H | mp. 164.2°C; .3/2(C ₂ H ₂ O ₄) |
| 52 | B.6 | CH ₃ | 3-O-(CH ₂) ₂ -CH ₃ | CH ₃ | H | H | .3/2(C ₂ H ₂ O ₄) |
| 53 | B.6 | CH ₃ | 3-O-CH-(CH ₃) ₂ | CH ₃ | H | H | mp. 133.9°C; .C ₂ H ₂ O ₄ .H ₂ O |
| 54 | B.14 | CH ₃ | 3-OH | CH ₃ | H | OH | - |
| 64 | B.10 | CH ₃ | 3-OH | CH ₃ | H | OH | .HCl.H ₂ O |
| 55 | B.6 | CH ₃ | 3-OH | CH ₃ | H | H | mp. >250°C |
| 57 | B.1 | CH ₃ | 2-OCH ₂ CH ₃ | CH ₃ | H | OH | - |
| 59 | B.13 | CH ₃ | 3-OCH ₂ CH ₃ | CH ₃ | H | NH ₂ | - |
| 95 | B.8a | CH ₃ | 3-OCH ₂ CH ₃ | CH ₃ | H | NH ₂ | (A) |
| 96 | B.8a | CH ₃ | 3-OCH ₂ CH ₃ | CH ₃ | H | NH ₂ | (B) |
| 62 | B.15 | CH ₃ | 3-O(CH ₂) ₂ N(CH ₃) ₂ | CH ₃ | H | OH | - |
| 63 | B.11 | CH ₃ | 3-O(CH ₂) ₂ -OH | CH ₃ | H | OH | - |
| 97 | B.1 | CH ₃ | 3-CH ₂ CH ₃ | CH ₃ | H | OH | - |
| 98 | B.13 | CH ₃ | 3-CH ₂ CH ₃ | CH ₃ | H | NH ₂ | mp. 240°C |
| 99 | B.1 | CH ₃ | 3-(CH ₂) ₂ CH ₃ | CH ₃ | H | OH | - |
| 100 | B.13 | CH ₃ | 3-(CH ₂) ₂ CH ₃ | CH ₃ | H | NH ₂ | - |
| 101 | * | CH ₃ | 3-O-(CH ₂) ₂ OCH ₃ | CH ₃ | H | OH | .3/2(C ₂ H ₂ O ₄) mp. 193°C |
| 102 | B.1 | CH ₃ | 3-CH ₃ | CH ₃ | H | OH | mp. >250°C |
| 103 | B.13 | CH ₃ | 3-CH ₃ | CH ₃ | H | NH ₂ | - |
| 104 | B.1 | CH ₃ | 3-Br | CH ₃ | H | OH | - |
| 105 | B.13 | CH ₃ | 3-Br | CH ₃ | H | NH ₂ | - |

| Co. No. | Ex. No. | R ¹ | R ² | R ^{4a} | R ⁵ | R ⁸ | Physical data |
|---------|---------|-----------------|---------------------------------|-----------------|-------------------|-----------------|---------------|
| 106 | B.1 | CH ₃ | 3-O-CF ₃ | CH ₃ | H | OH | - |
| 107 | B.13 | CH ₃ | 3-O-CF ₃ | CH ₃ | H | NH ₂ | mp. 168°C |
| 108 | B.1 | CH ₃ | 3-C ₆ H ₅ | CH ₃ | H | OH | - |
| 109 | B.13 | CH ₃ | 3-C ₆ H ₅ | CH ₃ | H | NH ₂ | - |
| 110 | B.1 | CH ₃ | 3-F | CH ₃ | H | OH | - |
| 111 | B.13 | CH ₃ | 3-F | CH ₃ | H | NH ₂ | mp. >250°C |
| 112 | B.1 | CH ₃ | 3-(E)-CH=CH-CH ₃ | CH ₃ | H | OH | mp. >250°C |
| 113 | B.2 | H | 3-Cl | CH ₃ | 3-Cl | OH | - |
| 114 | B.4 | CH ₃ | 3-Cl | CH ₃ | 3-Cl | OH | - |
| 115 | B.1 | CH ₃ | 3-Cl | H | 3-CH ₃ | OH | - |
| 116 | B.4 | CH ₃ | 3-Cl | CH ₃ | 3-CH ₃ | OH | - |
| 117 | ** | CH ₃ | 3-CN | CH ₃ | H | OH | - |
| 160 | B.1 | CH ₃ | 3-CF ₃ | CH ₃ | H | OH | - |

* : prepared by functional-group transformation of compound 54

** : prepared by functional-group transformation of compound 104

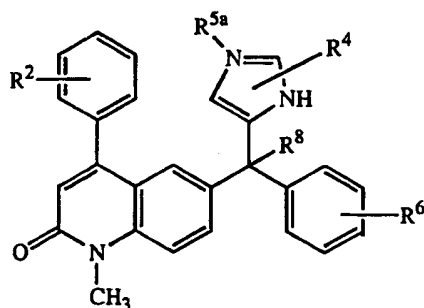
Table 3 :



5

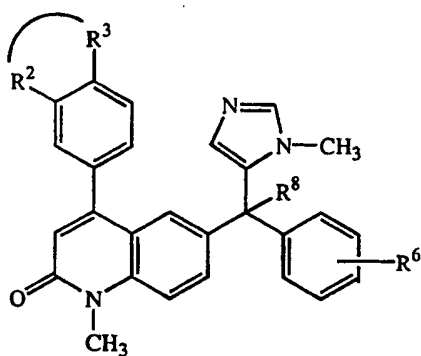
| Co. No. | Ex. No. | R ¹ | R ⁸ | Physical data |
|---------|---------|---|----------------|-------------------|
| 39 | B.4 | CH ₂ CONHCH(COOCH ₃)(CH ₂ CH(CH ₃) ₂) | H | mp. 240°C (S) |
| 40 | B.4 | CH ₂ -2-quinolinyl | H | mp. 240°C; .2 HCl |
| 41 | B.4 | CH ₂ CONHCH(COOCH ₃)(CH ₂ CH(CH ₃) ₂) | OH | mp. > 260°C (S) |

Table 4:



| Co. No. | Ex. No. | R ² | R ⁴ | R ^{5a} | R ⁶ | R ⁸ | Physical data |
|---------|---------|----------------|-------------------|---------------------------------|----------------|----------------|---|
| 42 | B.6 | H | H | H | 4-Cl | H | mp. 170°C; .C ₂ H ₂ O ₄ .1/2 H ₂ O |
| 43 | B.10 | H | H | H | 4-Cl | OH | mp. 180°C; .H ₂ O |
| 44 | B.5 | H | H | CH ₃ | 4-Cl | H | mp. 152°C |
| 45 | B.6 | 3-Cl | H | H | 4-Cl | H | mp. 175°C; .C ₂ H ₂ O ₄ |
| 46 | B.5 | 3-Cl | H | CH ₂ CH ₃ | 4-Cl | H | mp. 132°C; .C ₂ H ₂ O ₄ |
| 47 | B.5 | 3-Cl | H | CH ₃ | 4-Cl | H | mp. 115°C; .3/2 C ₂ H ₂ O ₄ |
| 48 | B.9 | 3-Cl | H | CH ₃ | 4-Cl | OH | mp. 230°C |
| 118 | B.4 | 3-Cl | 3-CH ₃ | CH ₃ | 4-Cl | OH | mp. 222°C |

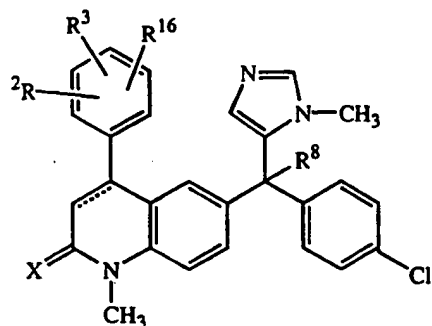
Table 5:



5

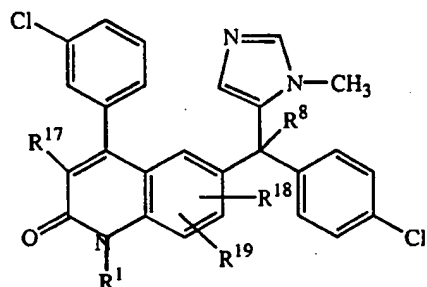
| Co. No. | Ex. No. | -R ² -R ³ - | R ⁶ | R ⁸ |
|---------|---------|---|----------------|-----------------|
| 119 | B.1 | -O-CH ₂ -O- | 4-Cl | OH |
| 120 | B.13 | -O-CH ₂ -O- | 4-Cl | NH ₂ |
| 121 | B.1 | -O-CH ₂ -CH ₂ -O- | 4-Cl | OH |
| 122 | B.13 | -O-CH ₂ -CH ₂ -O- | 4-Cl | NH ₂ |
| 123 | B.1 | -O-CH=CH- | 4-Cl | OH |

Table 6:



| Co. No. | Ex. No. | X | ----- | R ² | R ³ | R ¹⁶ | R ⁸ | Physical data |
|---------|---------|---|--------|--------------------|--------------------|--------------------|-----------------|--|
| 124 | B.1 | O | double | 3-OCH ₃ | 4-OCH ₃ | 5-OCH ₃ | OH | mp. 230°C |
| 125 | B.13 | O | double | 3-OCH ₃ | 4-OCH ₃ | 5-OCH ₃ | NH ₂ | mp. 218°C |
| 126 | B.1 | O | single | 3-Cl | H | H | OH | .C ₂ H ₂ O ₄ mp. 160°C |
| 127 | B.1 | O | single | 3-Cl | H | H | OH | - |
| 128 | B.16 | S | double | 3-Cl | H | H | H | - |

Table 7:

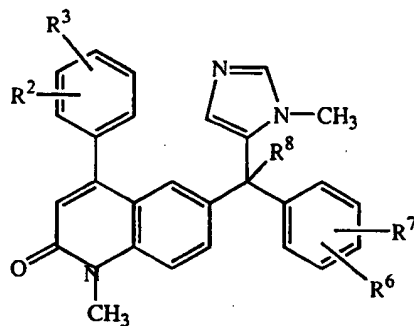


5

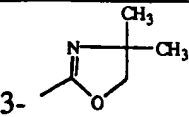
| Co. No. | Ex. No. | R ¹ | R ¹⁷ | R ¹⁸ | R ¹⁹ | R ⁸ | Physical data |
|---------|---------|-----------------|-------------------------------|-----------------|-----------------|---------------------|---------------|
| 129 | B.17 | H | CN | H | H | H | - |
| 130 | B.4 | CH ₃ | CN | H | H | H | mp. 202°C |
| 131 | B.17 | H | CN | H | H | OH | - |
| 132 | B.4 | CH ₃ | CN | H | H | OH | - |
| 133 | B.17 | H | CN | H | H | -CH ₂ CN | - |
| 134 | B.4 | CH ₃ | CN | H | H | -CH ₂ CN | mp. 138°C |
| 135 | B.18 | H | CH ₃ | H | H | OH | - |
| 136 | B.4 | CH ₃ | CH ₃ | H | H | OH | - |
| 137 | B.13 | CH ₃ | CH ₃ | H | H | NH ₂ | mp. >250°C |
| 138 | B.18 | H | C ₆ H ₅ | H | H | H | - |

| Co. No. | Ex. No. | R ¹ | R ¹⁷ | R ¹⁸ | R ¹⁹ | R ⁸ | Physical data |
|---------|---------|-----------------|-------------------------------------|--------------------|-------------------|-----------------|--|
| 139 | B.4 | CH ₃ | C ₆ H ₅ | H | H | H | .3/2(C ₂ H ₂ O ₄) mp. 180°C |
| 140 | B.18 | H | C ₆ H ₅ | H | H | OH | . |
| 141 | B.4 | CH ₃ | C ₆ H ₅ | H | H | OH | . |
| 142 | B.13 | CH ₃ | C ₆ H ₅ | H | H | NH ₂ | . |
| 143 | B.13 | CH ₃ | Cl | H | H | NH ₂ | . |
| 144 | B.17 | H | -COOCH ₂ CH ₃ | H | H | OH | . |
| 145 | B.4 | CH ₃ | -COOCH ₂ CH ₃ | H | H | OH | . |
| 146 | B.1 | CH ₃ | H | 8-CH ₃ | H | OH | . |
| 147 | B.13 | CH ₃ | H | 8-CH ₃ | H | NH ₂ | .H ₂ O |
| 148 | B.1 | CH ₃ | H | 7-Cl | H | OH | . |
| 149 | B.1 | CH ₃ | H | 7-CH ₃ | H | OH | . |
| 150 | B.1 | CH ₃ | H | 5-CH ₃ | H | OH | . |
| 151 | B.1 | CH ₃ | H | 8-OCH ₃ | H | OH | . |
| 161 | B.1 | CH ₃ | H | 7-CH ₃ | 8-CH ₃ | OH | mp. 255°C |

Table 8 :



| Co. No. | Ex. No. | R ² | R ³ | R ⁶ | R ⁷ | R ⁸ | Physical data |
|---------|---------|------------------------------------|----------------|------------------------------------|----------------|----------------|---|
| 152 | B.1 | 3-OCH ₂ CH ₃ | H | 4-OCH ₂ CH ₃ | H | OH | .3/2(C ₂ H ₂ O ₄) |
| 153 | B.1 | 3-Cl | H | H | H | OH | . |
| 154 | B.1 | 3-Cl | H | 4-CH ₃ | H | OH | . |
| 155 | B.1 | 3-Cl | H | 4-OCH ₃ | H | OH | . |
| 156 | B.1 | 3-Cl | H | 4-CF ₃ | H | OH | . |
| 157 | B.1 | 3-Cl | H | 2-Cl | 4-Cl | OH | . |
| 158 | B.1 | 3-Cl | 5-Cl | 4-Cl | H | OH | . |

| Co. No. | Ex. No. | R ² | R ³ | R ⁶ | R ⁷ | R ⁸ | Physical data |
|---------|---------|---|----------------|------------------------------------|----------------|----------------|---|
| 159 | B.1 |  | H | 4-Cl | H | OH | - |
| 162 | B.1 | 3-Cl | H | 4-S-CH ₃ | H | OH | mp. 169°C .C ₂ H ₂ O ₄ .H ₂ O; mp.decompose s > 172°C .C ₂ H ₂ O ₄ |
| 163 | B.1 | 3-Cl | H | 4-N(CH ₃) ₂ | H | OH | |
| 164 | B.1 | 3-Cl | H | -CH=CH-CH=CH- * | | OH | |

* : R⁶ and R⁷ taken together to form a bivalent radical between positions 3 and 4 on the phenyl moiety

Pharmacological example 1

- 5 Male athymic nude mice weighing approximately 22 to 25 g were inoculated subcutaneously in the inguinal region with 1×10^6 of LoVo human colon tumor cells (LoVo cells) on day 0. After three weeks to allow tumors to become established (diameter approximately 0.5 to 1 cm), treatment was started with solvent or compound 75 via the oral route, and either with or without a single shot irradiation on day 32.
- 10 Parameters for activity were tumor growth rate and weight of the tumors at day 42.

Compound 75 was dissolved in water and acidified with 1 N HCl solution to pH 2.5 and administered orally (po) as 0.1 ml of compound solution per 10 g mouse body weight twice daily (bid). The dose administered was either 50 or 100 mg compound per kg

15 bodyweight ; treatment either preceded irradiation (days 22-32), followed irradiation (days 32-42) or continued throughout the duration of the experiment (days 22-42).

Irradiation treatment consisted of a single dose of radiation on day 32 with a dose of 7 Gy that stabilized tumor growth in untreated animals, *i.e.* a dose that stopped the

20 increase in tumor volume, but did not cause any reduction in its size either.

The following table (Table 9) shows each of the arms that were evaluated in the experiment. In each arm of the experiment 16 animals were included. The column 'tumor (g)' contains the median of the tumor weight of the animals sacrificed at day 42

25 of the experiment. Figures 1 and 2 represent the observed data in graphical form.

Figure 1 shows the distribution of the tumor weights (g) of the test animals receiving 50 mpk of test compound (po, bid).

Figure 2 shows the distribution of the tumor weights (g) of the test animals receiving 100 mpk of test compound (po, bid).

The gray box in the figures depicts the 25-75 percentiles, the solid black line therein represents the median, the lines extending from the gray box depict the 10-90 percentiles and the black dots represent the outliers. The Roman numbers correspond to the groups of test animals as identified in Table 9.

From a statistical analysis of the data it follows that treatment with compound 75 (both 50 and 100 mpk) potentiates the effect of irradiation, more in particular that pretreatment with compound 75 (both 50 and 100 mpk) and irradiation reduces tumor weight in a statistically significant manner (when compared to irradiation alone).

Table 9

| Group | Compound 75 | treatment schedule | Irradiation | tumor (g) |
|-------|-------------|--------------------|-------------|---------------|
| I | solvent | day 22-42 | none | 0.475 |
| II | 50 mpk | day 22-42 | none | 0.255 |
| III | 50 mpk | day 22-32 | none | 0.273 |
| IV | 50 mpk | day 32-42 | none | 0.295 |
| V | 100 mpk | day 22-42 | none | 0.205 |
| VI | 100 mpk | day 22-32 | none | 0.234 |
| VII | 100 mpk | day 32-42 | none | 0.277 |
| VIII | 50 mpk | day 22-42 | 7 Gy | 0.207 |
| IX | 50 mpk | day 22-32 | 7 Gy | 0.156 |
| | | | | (p = 0.03)* |
| X | 50 mpk | day 32-42 | 7 Gy | 0.259 |
| XI | 100 mpk | day 22-42 | 7 Gy | 0.164 |
| | | | | (p = 0.0317)* |
| XII | 100 mpk | day 22-32 | 7 Gy | 0.141 |
| | | | | (p = 0.0022)* |
| XIII | 100 mpk | day 32-42 | 7 Gy | 0.214 |
| XIV | Solvent | day 22-42 | 7 Gy | 0.256 |

* Mann-Whitney U test vs Group XIV (radiotherapy only)

Example 2

Radioresistant human glioma cell lines (SF763, U87, U251) were treated with compound 75, 48 h prior to irradiation (2 Gy). The dose administered was 0.4 nM for U251 and 2 nM for SF763 and U87.

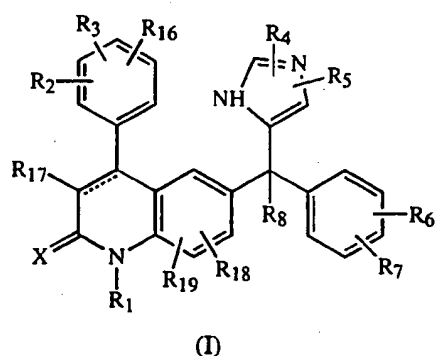
-29-

Applying compound 75 to the cells dramatically reduced the surviving of the cells after irradiation : for SF763 and U87, a decrease of surviving fraction of about 55 % was demonstrated, whereas for U251, the decrease was 25 %.

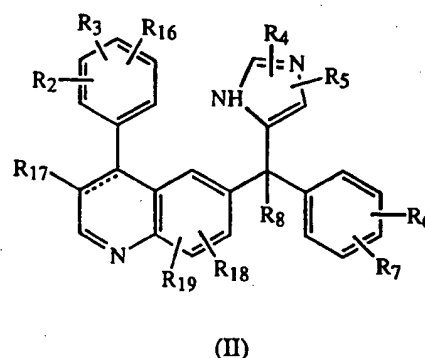
- 5 These results demonstrate that treatment with compound 75 resensitizes radioresistant cells to irradiation.

Claims

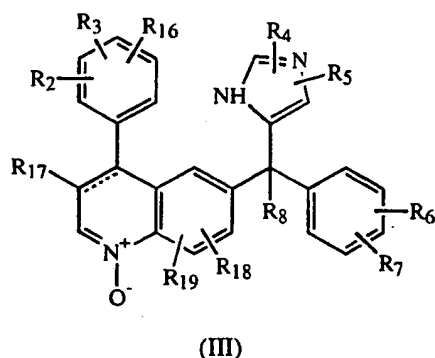
1. Use of at least a farnesyl protein transferase inhibitor for the preparation of a pharmaceutical composition having radiosensitizing properties for administration before, during or after irradiation of a tumor for treating cancer *in vivo*.
2. The use of claim 1 wherein said farnesyl protein transferase inhibitor is a compound of formula (I), or a compound of formula (II) or (III) which is metabolized *in vivo* to a compound of formula (I), said compounds being represent by



(I)



(II)



(III)

a stereoisomeric form thereof, a pharmaceutically acceptable acid or base addition salt thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

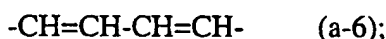
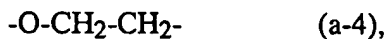
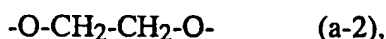
R¹ is hydrogen, C₁₋₁₂alkyl, Ar¹, Ar²C₁₋₆alkyl, quinolinylC₁₋₆alkyl, pyridyl-C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)-aminoC₁₋₆alkyl, aminoC₁₋₆alkyl,

or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹, wherein Alk¹ is C₁₋₆alkanediyl,

R⁹ is hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, amino, C₁₋₈alkylamino or C₁₋₈alkylamino substituted with C₁₋₆alkyloxycarbonyl;

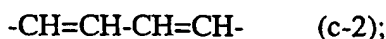
-31-

R², R³ and R¹⁶ each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, hydroxyc₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, amino-C₁₋₆alkyloxy, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar¹, Ar²C₁₋₆alkyl, Ar²oxy, Ar²C₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C₂₋₆alkenyl, 4,4-dimethyloxazoly; or when on adjacent positions R² and R³ taken together may form a bivalent radical of formula



R⁴ and R⁵ each independently are hydrogen, halo, Ar¹, C₁₋₆alkyl, hydroxy-C₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylS(O)C₁₋₆alkyl or C₁₋₆alkylS(O)₂C₁₋₆alkyl;

R⁶ and R⁷ each independently are hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, Ar²oxy, trihalomethyl, C₁₋₆alkylthio, di(C₁₋₆alkyl)amino, or when on adjacent positions R⁶ and R⁷ taken together may form a bivalent radical of formula



R⁸ is hydrogen, C₁₋₆alkyl, cyano, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonylC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, carboxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)-aminoC₁₋₆alkyl, imidazolyl, haloC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, or a radical of formula



wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

R¹¹ is hydrogen, C₁₋₁₂alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹² is hydrogen, C₁₋₆alkyl, C₁₋₁₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkylcarbonyl-

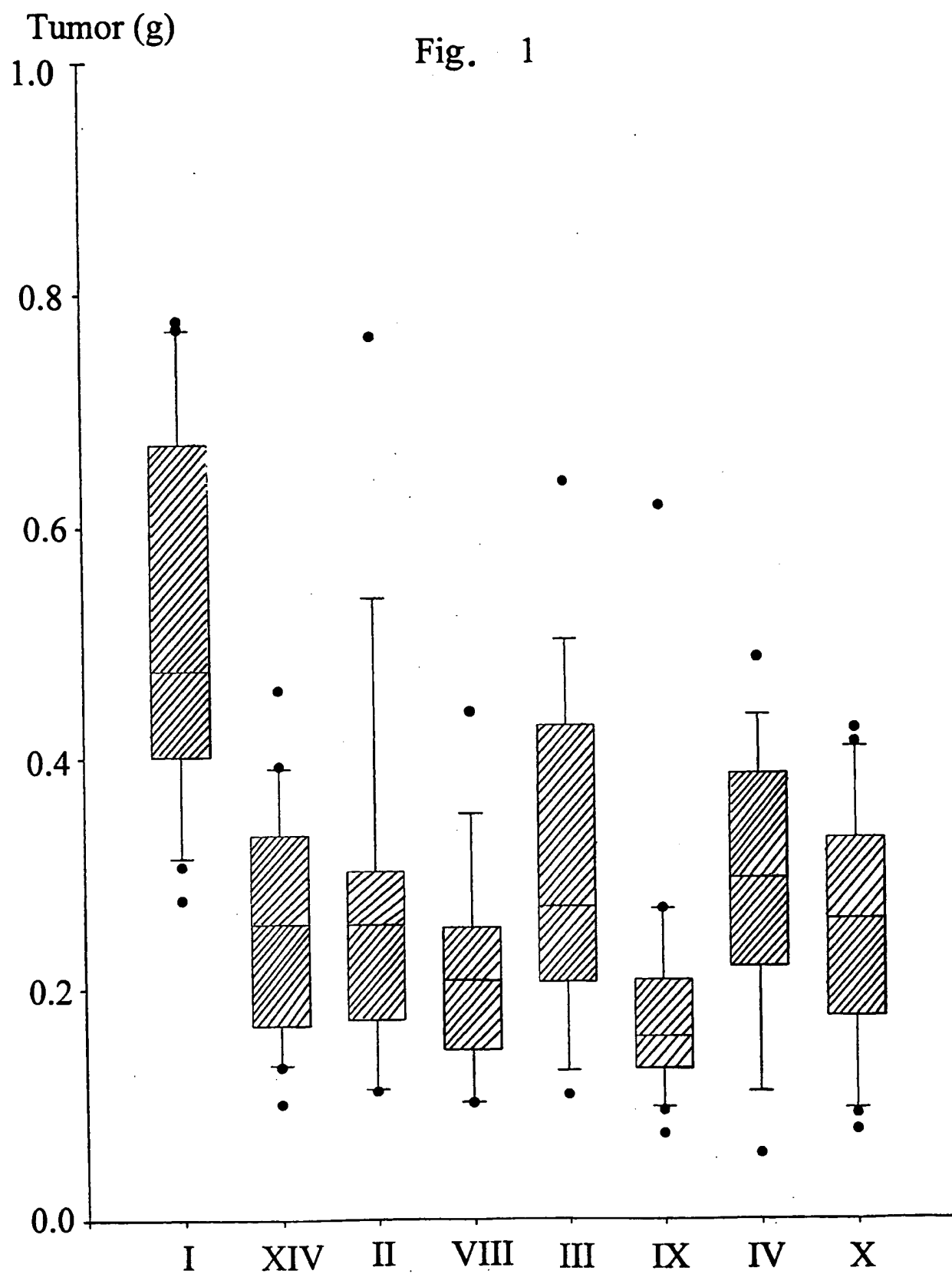
- C₁₋₆alkyl, a natural amino acid, Ar¹carbonyl,
 Ar²C₁₋₆alkylcarbonyl, aminocarbonylcarbonyl, C₁₋₆alkyloxy-
 C₁₋₆alkylcarbonyl, hydroxy, C₁₋₆alkyloxy, aminocarbonyl,
 di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, amino, C₁₋₆alkylamino,
 5 C₁₋₆alkylcarbonylamino,
 or a radical of formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;
 wherein Alk² is C₁₋₆alkanediyl;
 R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl,
 hydroxyC₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;
 10 R¹⁴ is hydrogen, C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;
 R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹ or
 Ar²C₁₋₆alkyl;
 R¹⁷ is hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, Ar¹;
 R¹⁸ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;
 15 R¹⁹ is hydrogen or C₁₋₆alkyl;
 Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy
 or halo; and
 Ar² is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy
 or halo.
 20
3. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 compound of formula (I) and wherein X is oxygen.
 4. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 25 compound of formula (I) and wherein the dotted line represents a bond.
 5. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 compound of formula (I) and wherein R¹ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy-
 C₁₋₆alkyl or mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl.
 30
 6. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 compound of formula (I) and wherein R³ is hydrogen and R² is halo, C₁₋₆alkyl,
 C₂₋₆alkenyl, C₁₋₆alkyloxy, trihalomethoxy or hydroxyC₁₋₆alkyloxy.
 7. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 35 compound of formula (I) and wherein R⁸ is hydrogen, hydroxy, haloC₁₋₆alkyl,
 hydroxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, imidazolyl, or
 a radical of formula -NR¹¹R¹² wherein R¹¹ is hydrogen or C₁₋₁₂alkyl and R¹² is

-33-

hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy, or a radical of formula -Alk²-OR¹³ wherein R¹³ is hydrogen or C₁₋₆alkyl.

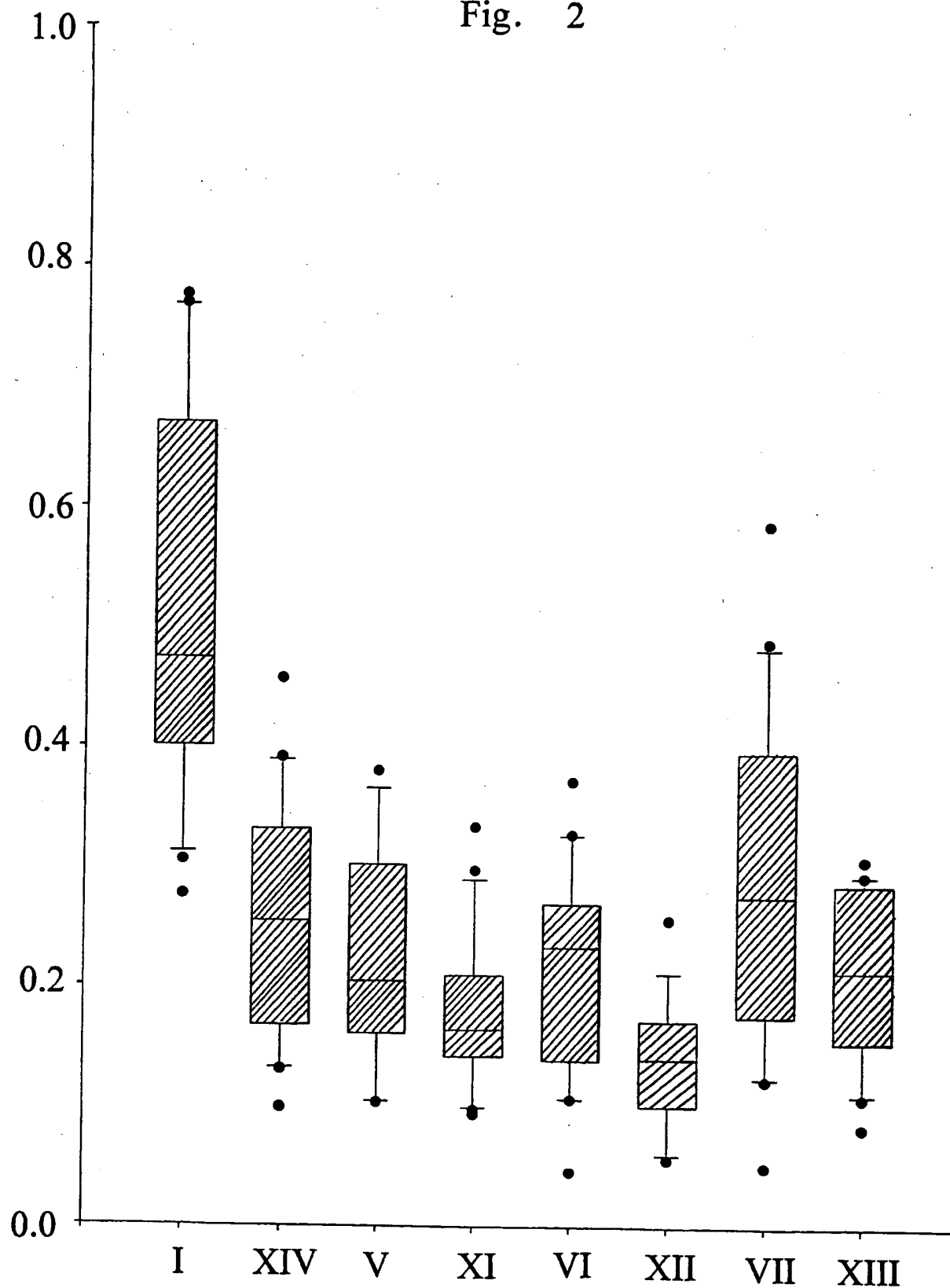
8. The use of claim 2 wherein the compound is
- 5 4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)-methyl]-1-methyl-2(1*H*)-quinolinone,
- 6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
- 10 6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone;
- 6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride.monohydrate;
- 15 6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone, and
- 6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salts thereof.
- 20 9. The use of claim 2 wherein the compound is
- (+)-(R)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone; or a pharmaceutically acceptable acid addition salt thereof.
- 25 10. The use of any one of the preceding claims wherein a therapeutically effective amount of the pharmaceutical composition is administered orally, parenterally, rectally or topically.
11. The use of claim 9 wherein the pharmaceutical composition is administered orally
- 30 in an amount of from 10 to 1500 mg/m² daily, either as a single dose or subdivided into more than one dose.
12. The use of claim 1 wherein the irradiation is ionizing irradiation.
- 35 13. The use of claim 1 wherein the irradiation of the tumor is external or internal.
14. The use of claim 1 wherein the administration of the pharmaceutical composition commences up to one month before the irradiation of the tumor.

15. The use of claim 1 wherein the irradiation of the tumor is fractionated and the administration of the pharmaceutical composition is maintained in the interval between the first and the last irradiation session.
- 5 16. A method of cancer therapy for a host harboring a tumor comprising the steps of
 - administering a radiation-sensitizing effective amount of a farnesyl protein transferase inhibitor before, during or after
 - administering radiation to said host in the proximity to the tumor.



Tumor (g)

Fig. 2



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04545

A. CLASSIFICATION OF SUBJECT MATTER
IPC-7 A61K41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | E.J. BERNARD ET AL: "The Farnesyltransferase Inhibitor FTI-277 Radiosensitizes H-ras-transformed Rat Embryo Fibroblasts." CANCER RESEARCH, vol. 56, 15 April 1996 (1996-04-15), pages 1727-1730, XP002118691 MD US page 1727, column 1, paragraph 1 --- | 1-16 |
| X | WO 97 38697 A (UNIV PENNSYLVANIA ;UNIV PITTSBURGH (US)) 23 October 1997 (1997-10-23) page 31, line 22 - line 23; claims page 25, line 10 - line 16 --- -/-- | 1-16 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

13 October 1999

Date of mailing of the international search report

12/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Berte, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04545

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | WO 97 16443 A (JANSSEN PHARMACEUTICA NV ;END DAVID WILLIAM (US); VENET MARC GASTO) 9 May 1997 (1997-05-09) claims ----- | |
| X | US 5 602 184 A (MYERS CHARLES E ET AL) 11 February 1997 (1997-02-11) column 6, line 1 - line 13; claims column 9, line 1 - line 13 ----- | 1,10-16 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 04545

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 16
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/04545

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|---|--|
| WO 9738697 A | 23-10-1997 | AU 2671697 A CA 2251716 A EP 0910385 A | 07-11-1997 23-10-1997 28-04-1999 |
| WO 9716443 A | 09-05-1997 | AU 7493396 A CN 1200732 A CZ 9801272 A NO 980928 A NZ 321576 A PL 328230 A SK 55698 A | 22-05-1997 02-12-1998 16-12-1998 29-04-1998 28-05-1999 18-01-1999 11-02-1999 |
| US 5602184 A | 11-02-1997 | AU 6276194 A WO 9420080 A | 26-09-1994 15-09-1994 |